Arthritis and Foodborne Bacteria

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ABSTRACT

Diarrheic episodes caused by the foodborne pathogens *Campylobacter*, *Salmonella*, *Shigella* or *Yersinia* may lead to a sterile arthritis such as reactive arthritis, Reiter's syndrome or ankylosing spondylitis. Reiter's syndrome and reactive arthritis have been shown to be sequelae in a few well-studied bacterial food poisoning outbreaks. Reactive arthritis, Reiter's syndrome and ankylosing spondylitis show strong familial association related to the gene for HLA-B27 (HLA = human leucocyte antigen) antigen. Why HLA-B27-positive individuals are more susceptible to arthritis is not known, but molecular mimicry between the HLA-B27 antigen and antigens of triggering bacteria has been demonstrated and this mimicry has been proposed as a mechanism involved in etiology of the arthritides. Antigens from bacteria that triggered the arthritis are present in arthritic joints but bacterial cells are not found. Antibodies and T-cells specific for the triggering bacteria have been demonstrated in arthritic patients. T-cells present in synovial joints respond specifically to the particular arthritic triggering pathogen. The cells that respond to bacterial antigens belong to the T-cell subset T_H1 that secrete a limited number of cytokines but it is not known if cytokines are involved in arthritis. A few studies have demonstrated that T-cells from the joints of arthritic patients respond to both bacterial and human heat shock proteins indicating that autoimmunity may be involved in causation of arthritis. While only about 2% of a population exposed to a triggering infection will acquire arthritis, these individuals undergo pain and suffering as well as economic hardships as a result of their disease.

Key Words: Arthritis, foodborne bacteria, *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia*.

Foodborne gastrointestinal pathogens may give rise to diseases that are far more serious than the temporary inconvenience of diarrhea and vomiting. For example, certain immunocompetent individuals may suffer chronic joint diseases such as reactive arthritis, Reiter's syndrome or ankylosing spondylitis after being infected with specific enteric pathogens. The relationship between diarrhea and chronic joint diseases has been reviewed by Archer (*3,4*), Archer and Kvenberg (*5*), Archer and Young (*6*) and Bunning et al. (*10*). These authors concluded that chronic sequelae do occur as a consequence of gastrointestinal disease and these sequelae add to the health and economic burden of afflicted individuals. The role of foodborne bacteria and their antigens as well as the role of genetics and other host factors on the induction and symptomology of the reactive arthritides are discussed in this review.

The reactive arthritides.

The reactive arthritides — reactive arthritis, Reiter's syndrome and ankylosing spondylitis — are characterized by disease of the sacroiliac joint, peripheral inflammatory arthritis and absence of rheumatoid factor. Other pathological effects may be seen in the entheses (sites of ligamentous insertion into bone), eye, aortic valve, lung parenchyma and skin. Clinically, the diseases have considerable overlap of symptoms. Clinical aspects of these arthritides are compared in Table 1. For a more complete discussion of the diseases, consult Aho et al. (*1*), Firestein and Zvaifler (*21*) and Kingsley (*42*) for reactive arthritis; Keat (*40*), Willkens et al. (*96*) and Yu (*100*) for Reiter's syndrome; and Ahern and Hochberg (*2*), Calin (*11,12*) and McGuigan et al. (*55*) for ankylosing spondylitis.

Triggering infections at non-articular sites by the enteric pathogens *Campylobacter jejuni, Salmonella typhimurium, Salmonella enteritidis, Shigella dysenteriae, Shigella flexneri, Shigalla sonnei* or *Yersinia enterocolitica* may lead to reactive arthritis or Reiter's syndrome (*26,29,35,40,49,61*). Salmonellae other than *S. enteritidis* and *S. typhimurium* induce the diseases but are rarely encountered (*58*). *Vibrio cholerae* and enteropathogenic or toxigenic *Escherichia coli* have not been implicated (*1*). The microorganisms that trigger reactive arthritis have the following features: (i) they infect mucosal surfaces, (ii) they have outer membrane lipopolysaccharides (LPS) and (iii) they are intracellular pathogens (*59*).

Infections probably trigger ankylosing spondylitis but proof is lacking. Elevated serum immunoglobulin A (IgA), clinical and immunogenetic similarities to reactive arthritis, and therapeutic response to sulfonamides suggest that bacterial infections may be involved (*56*). *Klebsiella* has been implicated in the etiology of the disease. Ebringer (*18*) cited evidence that he considered as proof that *Klebsiella* induces ankylosing spondylitis; however, Russell and Suarez Almazor (*74*) showed just as convincing evidence that the organism is not involved. The disease probably has a multifactorial cause involving the HLA-B27 antigen (see below) which interacts with unknown genetic, microbial and environmental factors. It must be emphasized that in the reactive arthritides, bacterial infections do not occur in the joints but rather at non-joint sites and the affected joints are sterile, e.g., viable pathogens are not isolated.

Medical scientists attending a radiology symposium in Sweden in 1990 were exposed to food contaminated with

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	Reactive arthritis	Reiter's syndrome	Ankylosing spondylitis
Sex distribution	male = female	male ≥ female	male ≥ female
Age at onset (years)	any age	≥ 20	≥ 20
Onset rate	sudden	sudden	gradual
Triggered by microbial infection	+	+	?
Arthritis in peripheral joints	lower > upper limb	lower limb, usually	lower limb, often
Spine involvement	+	+	+++
Sacroiliitis - inflammation of the articulation of the sacrum and ilium	++	++	+++
Urethritis - inflammation of the urethra	+	+	-
Inflammation of skin and mucous membranes	-	+	-
Inflammation of eye	+	+++	+
Rheumatoid factor	-	-	-
Familial aggregation	+	+	+
HLA-B27 positive (% of cases)	80-90	80-90	80-90
% risk for HLA-B27 positive individual	~20	10-20	10-20

Table modified from Calin (*12*).

S. enteritidis. Symptoms of salmonellosis was present in 108 of 113 individuals. Seventeen of the ill individuals (9 men and 8 women) developed reactive arthritis (*53*). In two recent outbreaks of foodborne salmonellosis in Canada, arthritis was detected in a number of diarrheic patients. In the first outbreak, a large group of policemen were exposed to *S. typhimurium* when they were served with contaminated food in a prepackaged box lunch (*35*). Of 116 infected men, 19 had developed joint disease of varying severity. In the second outbreak, 79 women and 4 men were present at a luncheon and 73 individuals developed salmonellosis. *Salmonella heidelberg* and *Salmonella hadar* was found in the potato salad that was served at the luncheon and *Salmonella thompson* was isolated from the stools of some patients (*90*). Six of the diarrheic patients subsequently developed reactive arthritis. In a large outbreak of milkborne salmonellosis in the United States, it was estimated that 168,000 to 198,000 individuals were ill (*75*). The incidence of reactive arthritis was reported to be 2.3% in patients with *Salmonella*-positive stools (*6*). Reiter's syndrome was estimated to be 10-fold less frequent than reactive arthritis. It is probable that a large number of cases of arthritis that were sequelae to this large *Salmonella* outbreak were not associated with the outbreak.

HLA-B27 antigen.

The genetic makeup of afflicted individuals may predispose them to reactive arthritis, Reiter's syndrome or ankylosing spondylitis since there is a familial association with the diseases (*40*). This familial association is related to the gene for the production of the HLA-B27 antigen which is part of the major histocompatibility complex.

In healthy populations, the HLA-B27 gene is found in 6 to 10% of Caucasians, 1% of Japanese and 2 to 4% of North American Blacks. The gene is absent in pure African Blacks and Australian Bushmen (*7,17,19,65*). About 2% of a population exposed to a triggering infection acquire arthritis but approximately 20% of the exposed HLA-B27-positive population will be affected (*1,12*). About 80% of the patients with reactive arthritis or Reiter's syndrome are HLA-B27-positive and they are likely to be more severely affected than HLA-B27-negative patients (*21,55*).

Most Caucasian patients with ankylosing spondylitis are HLA-B27-positive (96%), whereas only 80% of Mexican or Japanese, and 50% of Black ankylosing spondylitis patients are positive (*41*). Approximately 20% of HLA-B27-positive individuals will develop ankylosing spondylitis (*11*). Ankylosing spondylitis in HLA-B27-positive individuals is more severe than that seen in HLA-B27-negative patients (*2,52,72*); however, Singal (*85*) states that there are no significant differences in symptoms shown by HLA-B27-positive or -negative arthritic patients.

There are at least seven subtypes of HLA-B27 (*2,43,54,57*). For example, HLA-B2705 is present in 85 to 90% of Caucasian HLA-B27-positive individuals. HLA-B2704 and HLA-B2706 are found only in Orientals and HLA-B2703 is found only in North American Blacks. Individuals of all subtypes of HLA-B27 appear to be equally susceptible to arthritis. Studies by Breur-Vriesdendorp et al. (*9*) indicated that the HLA-B27 and ankylosing spondylitis correlation is not due to differences in the subtypes but is due to a shared common HLA-B27 determinant. Many HLA-B27-negative spondylitis patients have other HLA antigens which cross react with HLA-B27 antigen (*2,43,76*).

Cross-reactivity (molecular mimicry) between microorganisms and HLA-B27 molecules has been suggested as an explanation for the predominance of reactive arthritic diseases in HLA-B27-positive individuals. Thus, if a specific bacterial antigen is immunologically cross-reactive with a host antigen, an autoimmune reaction (arthritis) may result (*88*). Using polyclonal or monoclonal antibodies against HLA-B27 antigen, several workers have shown that there is cross-reactivity between a number of bacteria or their products and HLA-B27 (Table 2). However, other workers have not been able to show molecular mimicry between bacteria and HLA-B27 (*13,14,33*). These differences probably are due to variations in bacterial strains, procedures and assays used.

TABLE 2. *Cross-reactivity (mimicry) between HLA-B27 antigen and bacteria.*

Bacterial system that cross reacts with HLA-B27 antigen	Reference
K. pneumoniae, S. flexneri, Y. enterocolitica	*8*
Y. pseudotuberculosis	*15*
K. pneumoniae	*67*
S. flexneri, S. sonnei	*70*
Outer membrane protein (OMPA) of *E. coli, K. pneumoniae, Proteus mirabilis, S. typhimurium, S. heidelberg, S. flexneri, S. sonnei, Y. enterocolitica, Y. pseudotuberculosis*	*101*
Nitrogenase of *K. pneumoniae*	*81,82*
Outer membrane protein (YOPl) of *Y. enterocolitica, Y. pseudotuberculosis*	*93*
Plasmid PHS-2 from arthritogenic *S. flexneri*	*87,88*

Cross-reactivity between HLA-B27 and certain members of *Enterobacteriaceae* does occur, but the cross-reacting bacteria include species not known to be associated with the reactive arthritides. The finding that non-arthritogenic bacteria can cross-react with HLA-B27 antigen indicates that cross-reactivity is due to common antigens found in *Enterobacteriaceae* and that mimicry between bacteria and HLA-B27 may not be associated with the disease process itself (*66*). The presence of the HLA-B27 gene may merely influence the clinical appearance of the disease or its severity (*2,43*).

Antibodies, lymphocytes and bacterial antigens.

A less severe diarrhea is seen in patients who develop *Yersinia*-induced reactive arthritis. A mild diarrheic response leads to poor elimination of the infecting organism and thereby allows it to invade the intestinal mucosa and mesenteric lymph nodes (*92*). Intestinal biopsies indicated the presence of yersiniae in mucosal, submucosal and lymphoid tissue in the gut; in most cases, however, the bacteria were not cultivable (*44*). The deep location of the bacteria prevents them from being eliminated with feces and allows chronic stimulation of the gut-associated lymphatic system resulting in production of a *Yersinia*-specific immune response.

In arthritic patients with *Y. enterocolitica* enteritis, higher levels of *Yersinia*-specific IgG and IgA were present >12 months after infection (*91*). At 4 to 14 months after infection with *Salmonella*, patients with reactive arthritis had higher levels of *Salmonella*-specific IgA, IgG and IgM than patients not suffering from arthritis (*60*). Thus, persistence of antibody appears to be a common feature in *Yersinia* and *Salmonella* triggered reactive arthritis and indicates that the pathogen or its components persevere in the host.

Rheumatoid factor was not found in the circulation or joints of patients with *Yersinia*-triggered reactive arthritis but IgA and IgM immune complexes were present in a few patients (*46,47*). However, Inman et al. (*32*) were unable to demonstrate circulating IgA complexes in reactive arthritis or Reiter's syndrome patients. Thus, there appears to be some conflict concerning the presence of immune complexes in the reactive arthritides.

After infection by *Salmonella*, *Shigella* or *Yersinia*, specific microbial antigens (cellular and lipopolysaccharide) were found in synovial fluid cells and synovial membranes of patients with reactive arthritis (*26-28,62*). However, viable bacteria were not present in the arthritic joints. Viitanen et al. (*94*), using the polymerase chain reaction (PCR), were unable to find *Yersinia* DNA in synovial fluid cells of patients even though they were able to demonstrate *Yersinia* antigens in these cells. Non-detection of bacterial DNA would indicate absence of viable bacteria. Thus, antigens from triggering bacteria are present in the joints of arthritic patients but viable bacteria are not.

A presumed arthritogenic antigen from *Yersinia* is lipopolysaccharide (*27*). Skurnik et al. (*86*) have postulated that the β-subunit of *Y. enterocolitica* urease is an arthritogenic antigen also, since it induces arthritis in rats, and antibody against the subunit is found in human patients (*63*). *Yersinia enterocolitica* strains secreting the plasmid-mediated outer membrane protein, YadA, bind to cellular fibronectin (*80*). There was no binding to plasma (soluble) fibronectin. Cellular fibronectin is found in basement membranes and in connective tissue matrices. Since the fibronectin used in the study was purified from cartilage, the results suggest that YadA may bind to fibronectin of synovial joints and act as an arthritogenic antigen (*80*). Lipopolysaccharide from *S. enteritidis* or *S. typhimurium* (*28*) or *S. flexneri* (*26*) may be arthritogenic antigens, also.

The examination of proliferative responses (measured by incorporation of ^{3}H-thymidine) in helper T cells from synovial fluid of reactive arthritis patients revealed that the cells incorporated the greatest amount of isotope when they were exposed to the specific organism (*Campylobacter*, *Salmonella* or *Yersinia*) that had acted as the trigger for the arthritis (*25,30,84*). Cross reactions between triggering microorganisms suggested that they share common antigenic epitopes recognized by the T-cells.

Inman et al. (*34*) demonstrated that lymphocytes from patients with *S. typhimurium*-induced reactive arthritis were three-fold less responsive to *in vitro* stimulation with the triggering organism than were those from non-arthritic (but diarrheic) patients. Addition of exogenous interleukin-2 (IL-2) corrected the low proliferative response suggesting that there was minimal production of IL-2 in these arthritic patients (*34*). Also, the in vitro IgA, IgG and IgM production by cells from arthritic patients was several-fold less after stimulation with *Salmonella* than that in cells from non-arthritic patients (*34*). Thus, there appeared to be decreased lymphocyte proliferation and lower levels of IgA, IgG and IgM in patients with *S. typhimurium* -induced reactive arthritis. Previously, Leino et al. (*50*) and Vuento et al. (*95*) had demonstrated a lower proliferative response by T-lymphocytes to *Yersinia* in reactive arthritis patients.

Helper T-cells isolated from synovial fluid from HLA-B27-positive patients with *Yersinia*-induced reactive arthritis produced IFN-γ (gamma interferon) and IL-2 but not IL-4 or IL-5 when activated (*45,78*). Human T-cells recognizing antigens involved in the pathogenesis of several chronic inflammatory or allergic diseases exhibit a selective pattern of lymphokine secretion upon activation (*69,73,83,89*). The T_H1 subset of T-cells secretes IL-2, gamma interferon (IFN-γ) and lymphotoxin and executes cell-mediated immune responses (delayed hypersensivity and macrophage activation). The T_H2 subset secretes IL-4, -5, -6 and -10 and assists in antibody synthesis for humoral immune reactions. Thus, the *Yersinia* antigen selectively activated a subset of synovial joint T-cells that had a limited profile of cytokine secretion similar to T_H1 The presence of *Yersinia* antigen and *Yersinia*-reactive T_H1 T-cells within affected joints may be responsible for selective expansion of T_H1-cells with resultant generation and propagation of joint inflammation and arthritis (*45*).

More studies are needed to clarify the roles of bacterial antigens, antibodies and helper T-cells in joint inflammation and production of arthritis. In particular more information is needed concerning the functions that cytokines may play in the arthritic disease process.

Heat shock proteins.

Heat shock proteins (HSP), more properly known as stress proteins, are normal cell constituents which are produced in large amounts when prokaryotic or eukaryotic cells are subjected to stresses such as heat, chemicals, phagocytosis, etc. Stress proteins protect cells against harmful environmental conditions and are involved in protein transport and assembly as well as in other cellular activities. Heat shock proteins are cataloged on the basis of their molecular weights. Members of a particular HSP family are approximately the same in molecular weight and are similar in amino acid sequence and functions across species lines, e.g., they are highly conserved proteins. For example, cognates of the HSP60 family have a molecular weight of approximately 60 kDa, perform similar functions in animal, plant, yeast and bacterial cells and share more than 50% amino acid sequence homology. Various aspects of HSP have been reviewed by Ellis (*20*), Jaattela and Wissing (*36*), Kaufmann (*39*), Morimoto et al. (*64*) and Schlesinger (*79*).

Infection is stressful to both host and microbial cells. The metabolites produced by phagocytes ingesting microorganisms may induce HSP synthesis in both the microorganisms and phagocytes (*22,38*). Heat shock proteins are produced by microorganisms in an attempt to protect themselves from the noxious environment (reactive oxygen metabolites involved in the respiratory

burst) of the phagocytic interior. Additionally, phagocytic HSP protect phagocytes against their own reactive metabolites (*22,38*). Heat shock proteins, both microbial and host, are recognized by T-cells (*23,99*). Since the amino acid sequence of the stress proteins are similar in different species, a T-cell recognizing a microbial stress protein as antigen may act against a similar host stress protein with possible development of autoimmunity (*71*). There has been recent interest in the role of stress proteins in arthritis and other autoimmune diseases (for reviews see *16,23,97-99*).

Exposure of synovial T-cells from a *Salmonella*-induced reactive arthritis patient to antigenic fractions of *S. agona, E. coli* or a strain of *E. coli* with a plasmid for HSP60 synthesis demonstrated marked stimulation of T-cell proliferation by fractions in the 55 to 65 kDa range (*24,51*). These stimulatory fractions were probably HSP60. Synovial fluid T-cells isolated from a reactive arthritis patient gave proliferative responses to mycobacterial recombinant HSP65, *E. coli* HSP60, mycobacterial recombinant HSP70, *E. coli* HSP70 and HSP70 from heat-shocked human peripheral blood mononuclear cells (*48*). Hermann et al. (*31*), using synovial T-lymphocytes from a patient (HLA-B27-negative) with *Yersinia*-induced acute Reiter's syndrome, demonstrated that the lymphocytes responded to human HSP65 and *Mycobacterium bovis* HSP65. Hermann et al. (*31*) also found that there was a specific proliferative response of the T-cells to the patient's heat-shocked (42°C for 2 h) synovial cells. The stimulatory action of the heat-shocked host cells on the T-cell clone was probably due to HSP65 expressed by the heat-stressed cells. Thus, T-cells from the inflamed joints of reactive arthritis patients responded to both microbial and host HSP.

However, other studies indicate that HSP may not have an important role in the reactive arthritides. For example, Jarjour et al. (*37*) demonstrated that only 2 of 32 patients with Reiter's syndrome had IgG antibodies against human HSP60, HSP73 or HSP90; 0 of 32 of these patients had IgM activity against human HSP. None of 17 ankylosing spondylitis patients had IgG or IgM antibodies against the human HSP. Thus, IgM and IgG antibodies against human HSP appear to be uncommon in patients with Reiter's syndrome or ankylosing spondylitis. Probst el al. (*69*) were unable to demonstrate stimulation of T-cells from two patients with *Y. enterocolitica* -induced reactive arthritis by *Yersinia* HSP60.

Limited data suggest that synovial T-cells from joints of patients with reactive arthritis give proliferative responses to HSP and indicate that stress proteins induced in the invading pathogen may well be the antigens that trigger arthritis. The few studies which have been done on the role of host HSP in the reactive arthritides are conflicting since the results of Jarjour et al. (*37*) indicate that host HSP are not involved whereas the work of Hermann et al. (*34*) and Lamb et al. (*48*) suggest that immune reactions to host HSP may be important in these arthritides.

Economic considerations.

Nothing seems to have been published concerning the costs to individuals or to the community when reactive arthritis or Reiter's syndrome occurs after food poisoning outbreaks. In fact, the incidence of arthritis is seldom determined in outbreaks of *Campylobacter, Salmonella, Shigella* or *Yersinia* food poisoning.

In three recent outbreaks of *Salmonella* food poisoning that occurred in Sweden (one outbreak) and Canada (two outbreaks), the incidence and duration of arthritis was determined. Both the incidence and duration of arthritic symptoms have economic implications. *Salmonella enteritidis* contaminated food led to reactive arthritis in 17 of 108 scientists who became ill at radiology meeting in Sweden (*53*). Six months after the outbreak, five of the patients had complete resolution of their arthritic symptoms but in eight patients, the symptoms persisted (four patients could not be traced during follow-up). Approximately half of the patients were still suffering from reactive arthritis 6 months after the outbreak (*53*). Inman et al. (*35*) discussed a Canadian outbreak in which 1,608 policemen were exposed to *S. typhimurium*-contaminated food in prepackaged box lunches. The case definition for salmonellosis was met by 473 of the exposed individuals. Only 116 people were actually examined; 19 of these patients were shown to be arthritic. Inman et al. (*35*) classified 13 of the patients as having reactive arthritis and six as having Reiter's syndrome (arthritis and at least one extraarticular symptom) but the data in Table 3 would indicate that most of the 19 patients had Reiter's syndrome. Eleven of the patients agreed to HLA typing: four were HLA-B27 and six were HLA-B7, a HLA antigen that cross-reacts with HLA-B27 antigen. The data in Table 3 indicates that symptoms were resolved within 12 months in about half of the patients whereas arthritic symptoms persisted in the other patients and they were not symptom-free at 12 months (five patients could not be followed up after 1 year). Thomson et al. (*90*) discussed a second Canadian outbreak that occurred at a luncheon where 83 people (79 women and 4 men) were exposed to *Salmonella*-contaminated potato salad. There were 73 cases of salmonellosis. Six patients were classified at arthritic (five women and one man); five persons had reactive arthritis and one had Reiter's syndrome (arthritis and conjunctivitis). None of the individuals were HLA-B27-positive but two had HLA antigens that cross-reacted with HLA-B27. The data in Table 4 indicates that four of the patients had resolved their symptoms by 24 weeks but the other two had persistent symptoms lasting for longer than 24 weeks. It is not clear why patient 6 (Table 4) was classified as having reactive arthritis.

The mean age of the arthritic patients involved in the Swedish outbreak was 49 years (*53*) and the mean age of the Canadian arthritic patients listed in Tables 3 and 4 was approximately 40 years. Thus, these individuals were still in their active and produc-

TABLE 3. *Assessment of arthritic patients following a food poisoning outbreak involving* Salmonella-*contaminated food in prepackaged box lunches.*

Symptom	No. of patients	Symptoms resolved within 12 months	Symptoms persistent >12 months
Arthritis	19	8	7
Conjunctivitis	11	9	1
Urethritis	4	4	0
Dermatitis	4	3	1
Mucositis	2	2	0

Table modified from Inman et al. (*35*).

TABLE 4. *Assessment of arthritic patients following a food poisoning outbreak involving* Salmonella-*contaminated potato salad.*

Patient No.	No. of joints affected	Duration of symptoms in weeks
1	2	>24
2	10	>24
3	2	24
4	7	16
5	1	20
6	0	4

Table modified from Thomson et al. (*90*).

tive years but their arthritic condition probably precluded full-time gainful employment. The persistence of symptoms shown by the Swedish arthritic patients and the patients in Tables 3 and 4 suggest that these individuals visited their physicians often, probably were in pain for long periods and required frequent medication and were probably unable to work at full capacity. Thus, these particular individuals suffered more than a temporary and inconvenient salmonellosis but endured a painful and costly disease which represented an economic loss to themselves and to their communities.

CONCLUSIONS

While ankylosing spondylitis has not been shown to be triggered by infection, reactive arthritis or Reiter's syndrome may be induced when the individual is infected by foodborne microorganisms such as *Campylobacter*, *Salmonella*, *Shigella* and *Yersinia*. Reiter's syndrome and reactive arthritis have been shown to be sequelae in a few food poisoning outbreaks in which arthritis has been looked for.

Individuals who have the gene for HLA-B27 expression are more susceptible to the reactive arthritides. A considerable amount of effort has been expended on proving that molecular mimicry exists between the HLA-B27 antigen and bacterial antigens, but these studies have not increased our understanding of why HLA-B27-positive individuals are more vulnerable to arthritis. Saario et al. (*77*) have suggested that there may be increased permeability of the gut mucosa in HLA-B27-positive individuals and thus, there is increased uptake of bacterial antigens into the blood stream; these antigens eventually migrate to specific joints. However, nothing is really known concerning the basis for the susceptibility of HLA-B27-positive individuals to the reactive arthritides.

Bacterial antigens but not viable bacteria have been detected in the synovial fluid and cells of the joints of arthritic patients. How these antigens are disseminated from an infection at a non-joint site to the specific joints of the arthritic patient is unknown.

Both humoral and cellular immune responses are seen in arthritic patients. Immunoglobulin A and IgG antibodies persist much longer in patients with arthritis than in those who merely suffer from diarrhea and bacterial antigens from specific triggering bacteria are found in lymphocytes from arthritic joints. Since synovial T-cells from arthritic patients respond to the specific infecting organisms, it is possible that arthritis is mediated by T-cells and not by antibody. The type of T-cell that responds to the triggering antigens belong to the T-cell subset T_H1, which secrete mainly IL-2 and IFN-γ cytokines. The arthritic process may be related to secretion of these cytokines.

One of the more interesting areas in arthritides research is the role of HSP. Stimulation of joint T-lymphocytes by antigens from triggering microorganisms has been shown but the specific antigens have not been defined. It is possible that these antigens are HSP. While little work has been done concerning the role of HSP in pathogenesis of the reactive arthritides, a few studies have shown that synovial T-cells from reactive arthritis patients respond to microbial HSP *in vitro* proliferative assays. It is not clear whether synovial T-cells from arthritic patients respond to host HSP since conflicting results have been obtained. More studies are needed to clarify the role of both microbial and human HSP in the reactive arthritides.

For most individuals, infections by foodborne pathogens induce a transient and inconvenient disease but for the unfortunate few, the pathogens may trigger one of the reactive arthritides. An individual suffering from severe arthritis probably will undergo protracted and expensive medical treatment and will endure further economic hardship due to time lost from productive work.

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